Higher body mass index is associated with more adverse changes in calf muscle characteristics in peripheral arterial disease

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Objective: **This study investigated whether higher body mass index (BMI) is associated with more adverse lower extremity muscle characteristics at baseline and more adverse changes in muscle over time among participants with lower extremity peripheral arterial disease (PAD).**

Methods: **This was a longitudinal, observational study of 425 men and women with PAD and 261 without PAD. Computed tomography was used to measure calf muscle characteristics at baseline and every 2 years. Knee extension isometric strength, power, and 6-minute walk distance were measured at baseline and annually. Baseline BMI (kg/m^2) categories were ideal (20-25), overweight (>25-30), and obese (>30). Analyses adjust for age, race, sex, ankle brachial index, comorbidities, and other covariates.**

Results: **At baseline, higher BMI among participants with PAD was associated with greater calf muscle area (ideal BMI: 5181 mm^2; overweight: 5513 mm^2; obese: 5695 mm^2; $P = .0009$ for trend), higher calf muscle percentage of fat (6.38%, 10.28%, 17.44%, respectively, $P < .0001$ for trend), lower calf muscle density ($P < .0001$ for trend), and higher isometric knee extension strength ($P = .015$ for trend). Among participants with PAD, higher BMI was associated with greater declines in calf muscle area ($P = .030$ for trend) and greater increases in calf muscle percentage of fat ($P = .023$ for trend). Among participants without PAD, there were no significant associations of baseline BMI with changes in lower extremity muscle outcomes over time.**

Conclusions: **Among PAD participants, higher BMI is associated with greater calf muscle area at baseline. However, higher BMI is associated with more adverse calf muscle density and calf muscle percentage of fat at baseline and greater declines in calf muscle area over time. (J Vasc Surg 2012;55:1015-24.)**

Peripheral arterial disease (PAD) is a common, debilitating condition[1] and is associated with functional limitation and disability,[2,3] for which there are few effective treatments. Research has demonstrated that a higher body mass index (BMI) is associated with greater functional decline in people with PAD.[4] The pathophysiologic basis of this association is unclear. However, studies have demonstrated that adverse calf muscle characteristics are associated with greater functional impairment and faster functional decline in men and women with PAD.[5,6] These associations of higher BMI with greater functional decline in patients with PAD may be partly mediated by obesity-related changes in calf muscle composition. However, associations of higher BMI with calf muscle characteristics have not been reported previously in men and women with PAD.

We studied associations of baseline BMI with calf muscle area, calf muscle density, calf muscle percentage of fat, knee extension strength, and knee extension power among participants with PAD. We hypothesized that higher BMI would be associated with more adverse lower extremity muscle characteristics at baseline and more adverse changes in muscle characteristics over time. To determine whether associations identified were unique to individuals with PAD, we also studied associations of BMI with baseline muscle characteristics and changes in these characteristics over time among individuals without PAD. Finally, among participants with PAD, we used statistical modeling to determine whether associations of higher baseline BMI with more rapid functional decline in PAD may be mediated by higher baseline BMI with more adverse calf muscle characteristics, knee extension isometric strength, and knee extension power.

METHODS

The protocol for this study was approved by the Institutional Review Boards at Northwestern University Feinberg School of Medicine and Catholic Health Partners Hospital.

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Competition of interest: none.

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Patient identification. Participants were men and women with and without PAD participating in the Walking and Leg Circulation Study II (WALCS-II).[5] PAD participants were consecutively identified from three noninvasive vascular laboratories in the Chicago area.[5] A small number of PAD participants were identified from among patients in a general medical practice found to have a low ankle-brachial index (ABI), consistent with PAD.[5]

Participants without PAD were identified from among consecutive patients with normal results on lower extremity arterial tests in the vascular laboratory and from among consecutive patients in the general internal medicine practice who were found to have a normal ABI.[5]

Data were collected between November 6, 2002, and October 16, 2009. All participants gave written informed consent. Participants completed a baseline visit and up to four annual follow-up visits. Calf muscle characteristics were measured by computed tomography (CT) at baseline and at 2-year and 4-year follow-up assessments, and isometric knee extension strength and knee extension power were measured at baseline and at 1, 2, and 3 years.

Inclusion and exclusion criteria. Participants were aged 59 years or older at baseline. PAD was defined as ABI <0.90.[5] Absence of PAD was defined as an ABI of 0.90 to 1.30.[5] Exclusion criteria for WALCS-II have been described.[5] Exclusion criteria included an ABI ≥ 1.30, because these individuals could have stiffened lower extremity vessels, an ABI of 0.90 to 1.30 and history of lower extremity revascularization, individuals with a life expectancy <12 months, to allow for adequate follow-up, those with dementia, and those with a Mini-Mental Status Examination score of <23.[7] Participants who were nursing home residents, wheelchair-bound, or who had foot or leg amputations were excluded because of severely impaired functioning. Non–English-speaking patients were excluded because investigators were not fluent in non-English languages. Potential participants with BMI <20 kg/m^2 were excluded because of the small number who met this criterion and because BMI <20 kg/m^2 is typically classified distinctly from BMI 20 to 25 kg/m^2.

Body mass index. Height (in meters) and weight (in kilograms) were measured at baseline. Weight was remeasured at follow-up visits. BMI was calculated as kg/m^2. BMI categories (kg/m^2) were defined as ideal (20-25), overweight (>25-30), and obese (>30).

Ankle brachial index. After participants rested supine for 5 minutes, systolic pressures were measured using a hand-held Doppler probe (Nicolet Vascular Pocket Dop II, Golden, Colo) in the brachial, dorsalis pedis, and posterior tibial arteries of the right and left extremities. All pressures were measured twice. The ABI was calculated for each leg by dividing the average of the dorsalis pedis and posterior tibial artery pressures in each leg by the average of the four (ie, left and right) brachial pressures.[5] When one brachial pressure was higher than the opposite arm for both measurement sets, and the two brachial pressures differed by ≥ 10 mm Hg in at least one measurement set, the arm with highest pressure was used in the denominator for calculating the ABI for the left and right legs because subclavian stenosis was potentially present in these instances.[8] The same denominator was used for calculating the ABI in the left and right legs. Lowest leg ABI was included in analysis. Calf muscle characteristics were evaluated in the leg with lowest baseline ABI.

Calf muscle characteristics. Calf muscle characteristics were obtained using a CT scanner (LightSpeed; General Electric Medical Systems, Waukesha, Wisc). Cross-sectional images of the calves were obtained at 66.7% of the distance from the distal to the proximal tibia.[5] The muscle outline was traced manually on the cross-sectional CT images, excluding subcutaneous fat and bone, using BonAlyse software (BonAlyse OY, Jyvaskyla, Finland).[5,6] BonAlyse software quantifies muscle area by summing voxels corresponding to muscle (9-271 mg/cm^3) and excluding voxels corresponding to fat (-270 to 8 mg/cm^3).[5,6] Previous cadaveric studies have shown that estimates of muscle area using this method were highly correlated with direct anatomic measurements.[9] Intramuscular fat was quantified by summing voxels corresponding to fat within the demarcated muscle compartment. Muscle density is a measure of muscle quality and was calculated as the mean number of voxels within the range corresponding to muscle (9-271 mg/cm^3) per volume.

Isometric knee extension strength. Isometric knee extension strength was recorded using a computer-linked strength chair fitted with leg attachments and transducers to measure isometric knee extension over 5 seconds (Good Strength Chair; Metitur Oy, Jyvasklya, Finland).[10] Participants were instructed to build to their maximum strength over 2 seconds and maintain maximum strength for the final 3 seconds of the test. Maximum strength from two trials was used in analyses.[10]

Knee extension power. Knee extension power was obtained by asking subjects to push a footplate connected to a flywheel using maximal effort.[11] Final flywheel velocity was recorded by an optoswitch attached to a microcomputer and used to calculate knee extension power in Watts.[11] Five to nine trials were performed for each subject. Testing was stopped when the two highest power measurements were within 5% or when the participant had completed nine tests.[11]

Functional outcomes. Functional outcomes were measured using a standardized protocol at baseline and at each annual follow-up visit. The 6-minute walk distance (6MWD) was performed using standard methods.[2,3,5,6] The participant walked back and forth along a 100-foot hallway, after instructions to cover as much distance as possible.[2,3] The 4-meter walking velocity was recorded as walking velocity over 4 meters at "usual" and "fastest" walking speeds, respectively. The faster of two walks at each pace was included in analyses.[2,3,5,6,12]

Repeat chair rise was the time required for five consecutive rises from a seated position in a straight-backed

chair with arms folded across the chest.[12] Standing balance was recorded as the ability to perform three increasingly difficult standing positions for 10 seconds each, as previously described.[12]

The Short Physical Performance Battery (SPPB), with a score range of 0 to 12, was recorded as the sum of three separate scores (ranging, 0-4), assigned for performance in repeated chair rises, standing balance, and usual-paced 4-meter walking velocity. A score of 0 was assigned for any task a participant was unable to complete. Remaining scores for each task were based on quartiles of performance from >6,000 participants in the Established Populations for the Epidemiologic Study for the Elderly.[12]

Comorbidities. Comorbidities assessed were hypertension, diabetes mellitus, angina, myocardial infarction, stroke, heart failure, pulmonary disease, cancer, spinal stenosis, disk disease, and knee and hip osteoarthritis. Most comorbidities were documented using algorithms developed for the Women's Health and Aging Study and the Cardiovascular Health Study.[13] These comorbidity algorithms combined data from patient report, physical examination, medical record review, medications, laboratory values, and a primary care physician questionnaire. History of hypertension was based on a physician's indication of hypertension on the primary care physician questionnaire or patient report of physician-diagnosed hypertension. American College of Rheumatology criteria were used to identify knee and hip osteoarthritis.[14,15]

Other measures. Cigarette smoking was assessed by patient report. Activity level was by patient report of number of blocks walked. Occurrence of lower extremity revascularization, knee replacement surgery, or hip replacement surgery were measured during follow-up based on patient-report, medical record review, and a primary care physician questionnaire. If any of these sources reported hip or knee replacement surgery, the participant was considered to have had the procedure. Patient report of lower extremity revascularization required confirmation with medical record review or a primary care physician questionnaire.

Statistical analyses. Baseline characteristics of participants with and without PAD across the defined BMI categories were compared using χ^2 tests for categoric variables and general linear models for continuous variables. Among participants with and without PAD, respectively, analyses of covariance and statistical tests for trend were used to compare each baseline calf muscle characteristic, baseline knee extension strength, and baseline knee extension power across BMI categories, adjusting for age, race, sex, ABI (PAD participants only), smoking, physical activity, and comorbidities. We adjusted for tibia length in analyses of calf muscle area and knee extension measures.[16]

Associations of baseline BMI categories with average annual change in functional performance, calf muscle characteristics, knee extension strength, and knee extension power were analyzed using mixed-effects models, in which a subject-specific random effect was used to account for the potential correlations among successive annual differences in each outcome measure. Dependent variables in each mixed-effect regression analysis were the successive annual changes in functional performance and muscle outcomes, respectively. Analyses adjusted for age, race, sex, ABI (PAD participants only), smoking, comorbidities, activity level, tibia length (muscle area and knee extension measures only), lower extremity revascularization during follow-up, hip or knee replacement during follow-up, and prior year functional performance (for functional outcomes) or prior year muscle measure (for muscle outcomes).

Among participants with PAD, adjusted analyses of associations of baseline BMI with average annual functional decline were repeated with additional adjustments for baseline calf muscle percentage of fat, baseline calf muscle density, changes in calf muscle area, change in calf muscle percentage of fat, and all of these calf muscle measures simultaneously. These additional analyses were performed to determine whether associations of BMI with decline in functional performance were mediated by these muscle characteristics. In longitudinal analyses, BMI was a time-dependent variable, in which the BMI value used in analyses was updated for each follow-up visit. Statistical analyses were performed using SAS 9.2 software (SAS Institute Inc, Cary, NC).

RESULTS

Of 742 WALCS-II participants who completed baseline testing, 463 were PAD participants and 279 were non-PAD participants. The baseline analysis included 425 PAD subjects and 261 non-PAD subjects who met inclusion criteria (Fig 1). Of these, 357 with PAD and 229 without PAD were eligible for longitudinal analyses (Fig 1). Mean follow-up was 3.94 years.

Among the 425 PAD subjects who completed baseline testing, the average age was 74.9 ± 8.2 years, the mean ABI was 0.63 ± 0.15, and 104 (24%) had classic symptoms of intermittent claudication. Among the 261 participants without PAD who completed baseline testing, the average age was 71.5 ± 7.5 years and the mean ABI was 1.09 ± 0.09. Among participants with PAD, 57.2% were taking a cholesterol-lowering medication and 6% were taking cilostazol at baseline. Among participants without PAD, 30.7% were taking a cholesterol-lowering medication. Table I shows patient characteristics according to baseline BMI among participants with and without PAD. Higher BMI was associated with a higher prevalence of diabetes mellitus, greater calf muscle area, higher calf muscle percentage of fat, and lower calf muscle density among all participants. Among participants with PAD, higher BMI was also associated with younger age, higher isometric knee extension strength, and higher knee extension power. Among participants without PAD, higher BMI values were associated with African American race, lower ABI values, and a higher prevalence of knee osteoarthritis (Table I).

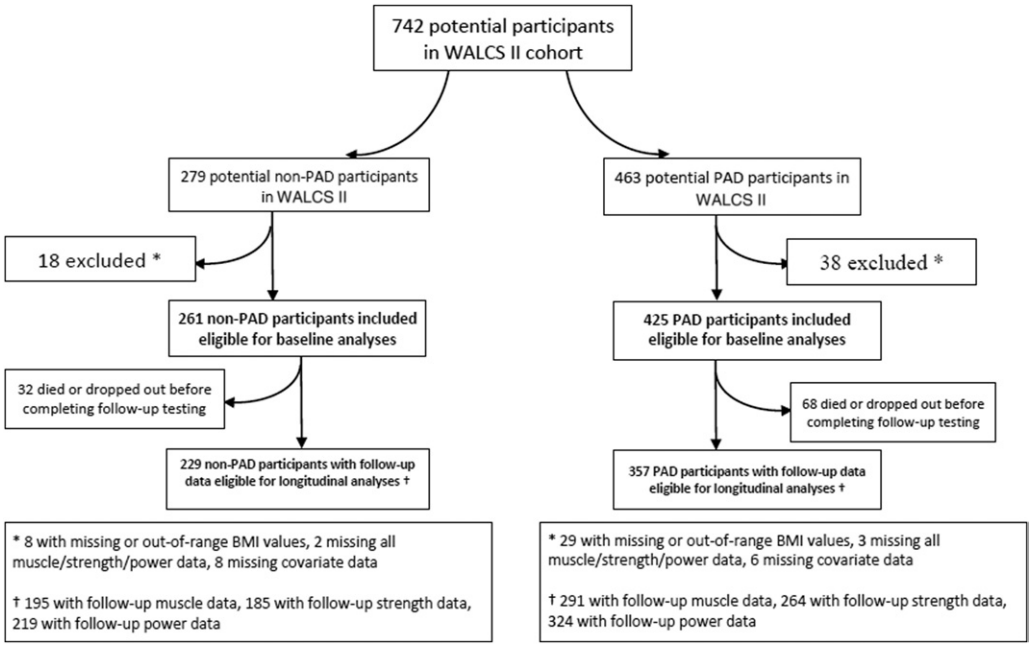

Fig 1. Flow chart shows participants with and without peripheral arterial disease (*PAD*) in the Walking and Leg Circulation Study II (*WALCS II*). *BMI,* Body mass index.

Table I. Baseline characteristics of 686 participants with and without peripheral arterial disease (*PAD*) according to baseline body mass index (*BMI*)

	Participants with PAD by BMI (kg/m²)				*Participants without PAD by BMI (kg/m²)*			
Variable[a]	*20-25 (n = 108)*	*25-30 (n = 184)*	*>30 (n = 133)*	P *(trend)*	*20-25 (n = 61)*	*25-30 (n = 95)*	*>30 (n = 105)*	P *(trend)*
Age, years	76.4 (8.9)	75.2 (8.6)	73.3 (6.7)	.003	72.9 (8.2)	71.5 (6.8)	70.6 (7.6)	.056
Black race	17.6	11.4	22.6	.232	8.2	23.2	23.8	.027
Male sex	43.5	63.0	54.1	.147	34.4	49.5	43.8	.355
Ankle brachial index	0.61 (0.15)	0.64 (0.15)	0.64 (0.16)	.202	1.12 (0.09)	1.10 (0.09)	1.06 (0.10)	<.001
Diabetes mellitus	23.2	30.4	46.6	<.001	13.1	15.8	36.2	<.001
Angina	30.2	39.0	36.4	.368	15.00	17.89	24.27	.134
Myocardial infarction	25.0	22.9	32.3	.169	14.8	11.6	18.1	.446
Stroke	25.9	19.6	22.6	.583	9.84	9.47	6.67	.440
Heart failure	25.9	28.3	34.6	.135	11.5	13.7	16.2	.393
Osteoarthritis								
Knee	13.0	9.2	17.3	.260	14.8	13.7	26.7	.035
Hip	4.6	0.00	7.5	.156	0.00	4.2	5.7	.089
Calf muscle								
Area, mm^2	4928 (901)	5649 (1388)	5742 (1687)	<.0001	5350 (1168)	5806 (1530)	6603 (1567)	<.0001
Density, gm/cm^3	33.4 (3.6)	33.2 (3.8)	30.9 (4.5)	<.0001	34.9 (3.8)	34.1 (3.6)	32.5 (4.1)	<.0001
Percentage of fat, %	7.1 (7.0)	9.9 (10.6)	17.3 (17.5)	<.0001	6.9 (9.9)	9.5 (12.0)	12.2 (12.8)	.005
Isometric knee extension strength, N	237 (85)	286 (112)	297 (118)	<.001	268 (97)	298 (133)	298 (109)	.177
Knee extension power, W	81 (41)	95 (50)	103 (60)	.002	104 (44)	128 (70)	115 (58)	.481

[a]Continuous variables are presented as mean (standard deviation) and categoric variables as percentage.

Fig 2 shows associations of baseline BMI with baseline calf muscle characteristics and knee extension strength among participants with PAD, adjusting for age, race, sex, ABI, smoking, comorbidities, physical activity, and tibia length (muscle area and knee extension measures only). Higher baseline BMI was associated significantly with higher calf muscle area and higher isometric knee extension strength and was also associated with higher calf muscle percentage of fat and lower calf muscle density.

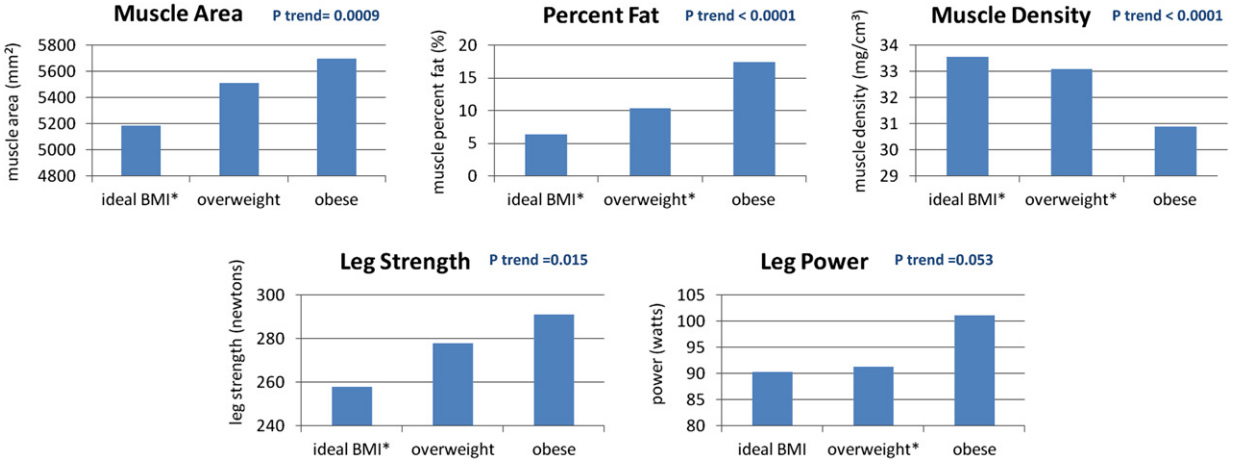

Fig 2. Adjusted associations of baseline body mass index (*BMI*) with baseline calf muscle characteristics among 425 men and women with peripheral arterial disease (PAD). **Data are adjusted for age, race, sex, ankle-brachial index, smoking, comorbidities, activity level, and tibia length (muscle area and knee extension measures only). BMI categories (kg/m^2) were defined as ideal (20-25), overweight (>25-30), and obese (>30). *Significant pair-wise comparison with obese BMI category. Pair-wise *P* values were <.001 (percent fat, muscle density), *P* = .0009 (muscle area), *P* = .014 (isometric knee extension strength), *P* = .048 (knee extension power). N = 412 for muscle area, percentage of fat, and muscle density analyses, n = 313 for leg strength analysis, and n = 384 for leg power analysis.

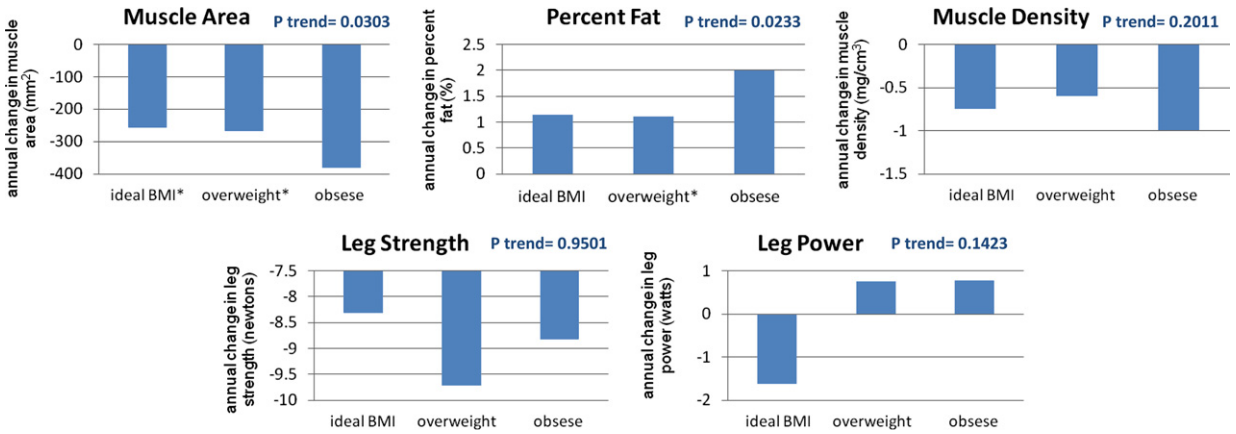

Fig 3. Adjusted associations of body mass index (*BMI*) with change in calf muscle characteristics among participants with peripheral arterial disease. **Data are adjusted for age, race, sex, ankle-brachial index, smoking, comorbidities, activity level, tibia length (muscle area and leg strength measures only), lower extremity revascularization during follow-up, hip or knee replacement during follow-up, and prior calf muscle characteristics. BMI categories (in kg/m^2) were defined as ideal (20-25), overweight (>25-30), and obese (>30). *Significantly different value compared with the obese BMI category. For muscle area, the pairwise *P* = .043 for the comparison between ideal BMI and obese. The pairwise *P* = .0254 for the comparison between overweight BMI and obese. For calf muscle percentage of fat, the pairwise *P* = .0261 for the comparison between obese and overweight. N = 291 for muscle area, percentage fat, muscle density analyses, n = 264 for leg strength analysis, and n = 324 for leg power analysis.

Fig 3 shows associations of BMI with average annual changes in lower extremity muscle characteristics, adjusting for age, race, sex, ABI, smoking, comorbidities, activity level, lower extremity revascularization during follow-up, hip or knee replacement surgery during follow-up, tibia length (muscle area and knee extension measures only), and prior year muscle measurements. Higher baseline BMI was associated with greater decline in calf muscle area (*P* = .030 for trend) and greater increase in calf muscle percentage of fat (*P* = .023 for

trend). There were no associations between higher baseline BMI and change in calf muscle density or leg strength measures (Fig 3).

Table II reports the associations of baseline BMI with average annual functional decline, adjusting for age, race, sex, ABI, smoking, comorbidities, activity level, lower extremity revascularization during follow-up, hip or knee replacement during follow-up, and prior year performance. Model 1a in Table II summarizes the associations of baseline BMI with average annual functional decline among participants with baseline calf muscle characteristic data. Higher baseline BMI was associated with greater declines in the SPPB ($P = .025$ for trend), usual-paced walking velocity ($P = .001$ for trend), fastest-paced walking velocity (P trend $< .001$), and 6MWD ($P = .002$ for trend; Model 1a, Table II). The significant association between higher BMI and greater decline in the SPPB was attenuated and no longer statistically significant after additional adjustment for baseline calf muscle percentage of fat and baseline calf muscle density (Table II).

Associations of higher baseline BMI with faster declines in walking velocity and the 6MWD were somewhat attenuated but remained highly statistically significant after additional adjustment for baseline calf muscle percentage of fat and baseline calf muscle density, respectively (Table II). These findings suggest that more adverse calf muscle percentage of fat and calf muscle density at baseline among more obese PAD participants may contribute to associations of higher baseline BMI with faster decline in the SPPB but may not contribute substantially to associations of higher baseline BMI with faster decline in walking velocity or the 6MWD.

Model 1a was repeated among participants with follow-up data on changes in calf muscle characteristics over time (Table II). When the sample size was limited to patients with follow-up calf muscle data, higher BMI was associated significantly with greater declines in the SPPB, the two measures of walking velocity, and the 6MWD (Table II, Model 1b). Associations of higher BMI values with greater declines in the SPPB and walking velocity remained statistically significant and were attenuated only to a small degree after adjusting for change in percentage of fat and change in calf muscle area. Associations of BMI with decline in the SPPB and usual-paced walking velocity were attenuated and no longer statistically significant after additional adjustment for baseline calf muscle measures and changes in calf muscle measures (Table II).

However, the association of BMI with decline in fast-paced 4-meter walking velocity and 6WMD remained statistically significant after adjustment for baseline calf muscle measures and changes in calf muscle measures (Table II). These findings suggest that associations of higher baseline BMI with more adverse calf muscle characteristics at baseline and changes in calf muscle over time may contribute to faster rates of decline in the SPPB among more obese PAD participants.

Among participants without PAD, higher BMI was associated with higher calf muscle area and lower calf muscle density at baseline, adjusting for age, race, sex, smoking, physical activity, comorbidities, and tibia length (calf muscle area and knee extension outcome only; Table III). Among participants without PAD, higher BMI was not associated with calf muscle percentage of fat or lower extremity strength measures after adjusting for confounders (Table III). Among participants without PAD, there were no associations of baseline BMI with change in lower extremity muscle measures over time, adjusting for age, sex, race, smoking, physical activity, comorbidities, prior year muscle measures, and hip or knee replacement during follow-up (Table III).

DISCUSSION

The results reported here demonstrate that higher baseline BMI was associated with a higher baseline calf muscle percentage of fat and lower baseline calf muscle density among men and women with PAD. However, higher baseline BMI was also associated with higher calf muscle area and better knee extension isometric strength. In longitudinal analyses, higher BMI at baseline was associated with greater decline in calf muscle area and greater increases in calf muscle percentage of fat, but not with significant changes in calf muscle density, knee extension isometric strength, or knee extension power compared with lower baseline BMI values. Among participants without PAD, higher BMI was associated with greater calf muscle area and lower calf muscle density at baseline. There were no associations of baseline BMI with change in lower extremity muscle characteristics over time among participants without PAD.

The association of higher BMI with lower baseline calf muscle density at baseline among participants with and without PAD and the association of higher BMI with greater baseline calf muscle percentage of fat at baseline among individuals with PAD may reflect poorer muscle quality in obese participants with and without PAD, despite higher muscle quantity, measured by greater calf muscle area. The associations of higher BMI with higher calf muscle area among participants with and without PAD and the association of higher BMI with better knee extension strength among participants with PAD at baseline may reflect the need for greater muscle quantity or strength to support heavier body weight in obese individuals. Higher muscle area may compensate for lower muscle density (ie, poorer muscle quality) among obese participants.

Among participants with PAD, higher baseline BMI was associated with greater declines in the SPPB score, usual and fast-paced walking velocity, and 6MWD after adjusting for confounders. The association of higher BMI with faster decline in the SPPB was attenuated after additional adjustment for the adverse calf muscle characteristics associated with higher BMI values. This finding suggests that adverse associations of BMI with baseline calf muscle characteristics and changes in these characteristics over time

Table II. Baseline body mass index (*BMI*) and functional decline among participants with peripheral arterial disease (*PAD*)

Variable[a]	*BMI (kg/m²)*			P
	20-25	*25-30*	*>30*	*(trend)*
Associations of BMI with functional decline with and without additional adjustment for baseline calf muscle characteristics				
Short physical performance battery decline (n = 304)	*(n = 76)*	*(n = 138)*	*(n = 90)*	
Model 1a	−0.32 (−0.53 to −0.11)	−0.35 (−0.53 to −0.17)	−0.57 (−0.78 to −0.37)	.025
Plus adjustment for baseline percent fat	−0.35 (−0.57 to −0.136)	−0.35 (−0.54 to −0.17)	−0.52 (−0.732 to −0.32)	.159
Plus adjustment for baseline calf density	−0.33 (−0.55 to −0.117)	−0.36 (−0.54 to −0.17)	−0.55 (−0.753 to −0.34)	.064
Usual walking velocity decline, m/s (n = 337)	*(n = 81)*	*(n = 152)*	*(n = 104)*	
Model 1a	−0.03 (−0.04 to −0.01)	−0.04 (−0.05 to −0.02)	−0.05 (−0.06 to −0.04)	.001
Plus adjustment for baseline percent fat	−0.03 (−0.04 to −0.02)	−0.04 (−0.05 to −0.02)	−0.05 (−0.06 to −0.03)	.004
Plus adjustment for baseline calf density	−0.03 (−0.04 to −0.01)	−0.04 (−0.05 to −0.02)	−0.05 (−0.06 to −0.04)	.002
Fastest walking velocity decline, m/s (n = 332)	*(n = 81)*	*(n = 149)*	*(n = 102)*	
Model 1a	−0.02 (−004 to −0.01)	−0.03 (−0.05 to −0.01)	−0.05 (−0.06 to −0.03)	<.001
Plus adjustment for baseline percent fat	−0.02 (−0.04 to −0.01)	−0.03 (−0.05 to −0.01)	−0.05 (−0.06 to −0.03)	.001
Plus adjustment for baseline calf density	−0.02 (−0.04 to −0.01)	−0.03 (−0.05 to −0.02)	−0.05 (−0.06 to −0.03)	.001
6-minute walk distance decline, feet (n = 323)	*(n = 80)*	*(n = 146)*	*(n = 97)*	
Model 1a	−32.2 (−57.4 to −7.1)	−45.7 (−66.1 to −25.3)	−76.3 (−101.0 to −51.7)	.002
Plus adjustment for baseline percent fat	−33.2 (−58.7 to −7.8)	−45.6 (−66.13 to −25.1)	−74.9 (−100.0 to −49.8)	.004
Plus adjustment for baseline calf density	−32.3 (−57.6 to −7.0)	−45.7 (−66.22 to −25.2)	−76.2 (−101.3 to −51.1)	.002
Associations of BMI with functional decline with and without additional adjustment for changes in calf muscle characteristics over time				
Short physical performance battery decline (n = 234)	*(n = 57)*	*(n = 109)*	*(n = 68)*	
Model 1b	−0.74 (−1.3 to −0.24)	−0.86 (−1.4 to −0.38)	−1.1 (−1.6 to −0.62)	.003
Plus adjustment for change in percentage of fat	−0.75 (−1.3 to −0.26)	−0.86 (−1.3 to −0.38)	−1.1 (−1.6 to −0.62)	.006
Plus adjustment for change in calf area	−0.77 (−1.3 to −0.28)	−0.86 (−1.3 to −0.39)	−1.1 (−1.5 to −0.60)	.012
Plus baseline muscle density, baseline percent fat, change in percent fat, change in muscle area	−0.82 (−1.3 to −0.32)	−0.89 (−1.4 to −0.41)	−1.1 (−1.5 to −0.58)	.081
Usual walking velocity decline, m/s (n = 257)	*(n = 60)*	*(n = 120)*	*(n = 77)*	
Model 1b	−0.02 (−0.05 to 0.02)	−0.02 (−0.06 to 0.01)	−0.04 (−0.07 to −0.00)	.017
Plus adjustment for change in percentage of fat	−0.02 (−0.05 to 0.02)	−0.02 (−0.06 to 0.01)	−0.04 (−0.07 to −0.00)	.019
Plus adjustment for change in calf area	−0.02 (−0.05 to 0.02)	−0.02 (−0.05 to 0.01)	−0.04 (−0.07 to −0.00)	.023
Plus baseline muscle density, baseline percent fat, change in percent fat, change in muscle area	−0.02 (−0.05 to 0.02)	−0.02 (−0.05 to 0.01)	−0.03 (−0.07 to 0.00)	.061

Table II. Continued

Variable[a]	*BMI (kg/m²)* 20-25	25-30	>30	P *(trend)*
Fastest walking velocity decline, m/s (n = 256)	*(n = 60)*	*(n = 119)*	*(n = 77)*	
Model 1b	−0.03 (−0.07 to 0.01)	−0.05 (−0.08 to −0.01)	−0.05 (−0.09 to −0.01)	.009
Plus adjustment for change in percentage of fat	−0.03 (−0.07 to 0.01)	−0.04 (−0.08 to −0.01)	−0.05 (−0.09 to −0.01)	.01
Plus adjustment for change in calf area	−0.03 (−0.07 to 0.01)	−0.04 (−0.08 to −0.01)	−0.05 (−0.09 to −0.01)	.01
Plus baseline muscle density, baseline percent fat, change in percent fat, change in muscle area	−0.03 (−0.07 to 0.01)	−0.04 (−0.08 to −0.00)	−0.05 (−0.09 to −0.01)	.013
6-minute walk distance decline, ft (n = 252)	*(n = 60)*	*(n = 116)*	*(n = 76)*	
Model 1b	−23.5 (−66.8 to 19.9)	−37.8 (−78.1 to 2.6)	−64.7 (−107.3 to −22.1)	.0109
Plus adjustment for change in percentage of fat	−21.8 (−64.8 to 21.3)	−34.9 (−75.1 to 5.3)	−61.4 (−103.8 to −18.9)	.013
Plus adjustment for change in calf area	−21.5 (−64.7 to 21.7)	−35.5 (−75.8 to 4.8)	−61.3 (−103.9 to −18.6)	.012
Plus baseline muscle density, baseline percent fat, change in percent fat, change in muscle area	−24.1 (−67.3 to 19.2)	−35.1 (−75.2 to 5.0)	−60.4 (−103.0 to −17.5)	.037

[a]Data shown are average annual decline in functional performance and 95% confidence intervals across baseline BMI categories. Model 1 adjusts for age, race, sex, ankle brachial index, smoking, comorbidities, physical activity, lower extremity revascularization during follow-up, hip or knee replacement during follow-up, and prior year performance. Model 1a is limited to all participants with baseline muscle data. Model 1b is limited to participants with follow-up muscle data.

Table III. Associations of body mass index (*BMI*) with baseline lower extremity muscle characteristics and change in lower extremity muscle characteristics among participants without peripheral arterial disease (PAD)

Variable	*BMI (kg/m²)* 20-25	25-30	>30	P *(trend)*
Baseline data[a]				
Muscle area (mm²)	n = 60 5401 (5070-5732)	n = 92 5731 (5474-5988)	n = 104 6636 (6387-6885)	<.001
Percent fat	n = 60 8.42 (5.33-11.50)	n = 93 9.34 (6.96-11.73)	n = 104 11.46 (9.14-13.78)	.117
Muscle density	n = 60 34.5 (33.5-35.4)	n = 93 34.1 (33.4-34.9)	n = 104 32.8 (32.1-33.5)	.005
Isometric knee extension strength	n = 51 277 (252-301)	n = 78 293 (274-312)	n = 83 297 (278-316)	.226
Leg power	n = 56 107 (94-120)	n = 85 125 (115-135)	n = 99 117 (107-126)	.404
Longitudinal data [b]				
Muscle area (mm²)	n = 45 −239 (−320 to −158)	n = 69 −229 (−291 to −168)	n = 80 −289 (−350 to −228)	.214
Percent fat	n = 45 1.14 (0.47 to 1.81)	n = 70 1.09 ([0.58 to 1.59)	n = 80 1.48 (1.00 to 1.97)	.112
Muscle density	n = 45 −0.70 (−1.09 to −0.31)	n = 70 −0.32 (−0.61 to −0.03)	n = 80 −0.65 (−0.94 to −0.37)	.456
Isometric knee extension strength	n = 43 −8.60 (−16.70 to −0.49)	n = 70 −7.39 (−12.98 to −1.80)	n = 72 −3.96 (−10.46 to 2.54)	.875
Leg power	n = 50 −4.68 (−9.09 to −0.27)	n = 77 −1.25 (−4.60 to 2.11)	n = 92 −0.26 (−3.54 to 3.03)	.388

[a]Baseline associations are adjusted for age, sex, race, smoking, physical activity, comorbitities (calf muscle area outcome only). Values are shown with 95% confidence intervals.

[b]Longitudinal associations (i.e., average annual change in each leg muscle measure) are adjusted for age, sex, race, smoking, physical activity, comorbidities, prior year muscle measurement, and hip or knee replacement during follow-up. Values are shown with 95% confidence intervals.

may partially explain associations of higher BMI with greater declines in the SPPB. However, among participants with PAD, associations of higher BMI with faster declines in walking velocity and the 6MWD were not substantially attenuated by additional adjustments for baseline adverse muscle characteristics or changes in muscle characteristics associated with higher BMI values. Thus, these associations of higher BMI with faster declines in walking velocity and the 6MWD are not likely to be explained by the associations of higher BMI with more adverse calf muscle characteristics at baseline or changes in these characteristics over time.

Our findings suggest, for the first time, that obesity is associated with lower calf muscle density, higher calf muscle percentage of fat, and greater declines in calf muscle area as measured by CT in men and women with PAD. The combination of PAD with higher BMI values may be particularly adverse because higher BMI values were associated with greater declines in calf muscle area and greater increases in calf muscle percentage of fat only among participants with PAD but not among participants without PAD.

The significance of the faster decline in calf muscle area among PAD participants with higher baseline BMI is unclear because obese participants with PAD did not experience a greater decline in knee extension strength or knee extension power. However, our longitudinal measures of lower extremity strength did not include changes in plantar flexion, which is expected to better reflect declines in calf muscle area over time, because calf muscle is responsible for plantar flexion strength while muscles proximal to the calf are responsible for knee extension.

This study has some limitations:

1. The study is observational, and causal inferences cannot be made.
2. Of the 425 eligible PAD participants who completed baseline testing, only 357 had follow-up data for these analyses.
3. Although our cohort was monitored prospectively for 4 years, longer follow-up may be needed to detect additional adverse changes in lower extremity muscle associated with obesity in PAD.
4. We did not have longitudinal data on plantarflexion strength.
5. We did not have data on insulin resistance, which may be a mediator of the associations reported here.
6. We did not collect CT images of upper extremity muscle. Therefore, we cannot determine whether associations of baseline BMI with changes in lower extremity muscle characteristics are unique to the lower extremities.

CONCLUSIONS

Higher BMI is associated with more adverse calf muscle density and percentage of fat at baseline and greater decline in calf muscle area at 4-year follow-up among men and women with PAD. Further investigation is needed to determine whether weight loss among obese patients with PAD can protect against adverse muscle characteristics at baseline and adverse changes in calf muscle characteristics over time. Our study suggests that PAD patients should be encouraged to maintain an ideal body weight.

AUTHOR CONTRIBUTIONS

Conception and design: MM, KL, LT, LF, JG, MC
Analysis and interpretation: KL, YL, MM, ZR, LT, LF, JG, MC
Data collection: MM, KL, LF, JG, MC
Writing the article: ZR, MM
Critical revision of the article: KL, YL, MM, ZR, LT, LF, JG, MC
Final approval of the article: KL, YL, MM, ZR, LT, LF, JG, MC
Statistical analysis: KL, LT, YL
Obtained funding: MM, KL, LF, JMG, MC
Overall responsibility: MM

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